

Listing of Claims

1. (original) An herpes simplex virus wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous nitroreductase (NTR).
2. (currently amended) The~~An~~ herpes simplex virus as claimed in claim 1 wherein said NTR is *E. coli* NTR.
3. (currently amended) The~~An~~ herpes simplex virus as claimed in claim 2 wherein said nucleic acid comprises SEQ ID No. 2 or nucleic acid encoding the polypeptide of SEQ ID No. 1.
4. (currently amended) The~~An~~ herpes simplex virus as claimed in claim 1 wherein said nucleic acid:
 - (a) has at least 60% sequence identity to SEQ ID No. 2 or to a nucleic acid encoding the polypeptide~~polypeptide~~ of SEQ ID No. 1;
 - (b) has at least 70% sequence identity to SEQ ID No. 2 or to a nucleic acid encoding the polypeptide~~polypeptide~~ of SEQ ID No. 1; or
 - (c) hybridises to the nucleic acid of SEQ ID No. 2, to its complement or to a nucleic acid encoding the polypeptide~~polypeptide~~ of SEQ ID No. 1 under high stringency conditions.
5. – 6. (cancelled)
7. (currently amended) The~~An~~ herpes simplex virus according to any one of claims~~claim~~ 1 to 6 wherein said herpes simplex virus genome further comprises a regulatory nucleotide sequence operably linked to said nucleic acid encoding NTR, wherein said regulatory nucleotide sequence has a role in controlling transcription of said NTR.
8. (currently amended) The~~An~~ herpes simplex virus as claimed in any one of claims~~claim~~ 1 to 7 wherein said nucleic acid is located in at least one RL1 locus of the herpes simplex virus genome.

9. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 8-wherein said nucleic acid is located in, or overlaps, at least one of the ICP34.5 protein coding sequences of the herpes simplex virus genome.

10. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 9-wherein the herpes simplex virus is a mutant of one of HSV-1 strains 17 or F or HSV-2 strain HG52.

11. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 9-wherein the herpes simplex virus is a mutant of HSV-1 strain 17 mutant 1716.

12. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 11-which is a gene specific null mutant.

13. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 12-which is an ICP34.5 null mutant.

14. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 11-which lacks at least one expressible ICP34.5 gene.

15. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 10-which lacks only one expressible ICP34.5 gene.

16. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 15-which is non-neurovirulent.

17. (currently amended) The An herpes simplex virus as claimed in any one of claims of claim 1 to 16-wherein said nucleic acid encoding the heterologous nitroreductase (NTR) forms part of a nucleic acid cassette integrated in the genome of said herpes simplex virus, said cassette encoding:

(a) said nucleic acid encoding NTR; and nucleic acid encoding

(b) a ribosome binding site; and

(c) a marker,

wherein the nucleic acid encoding NTR is arranged upstream (5') of the ribosome binding site and the ribosome binding site is arranged upstream (5') of the marker.

18. (currently amended) The An herpes simplex virus according to claim 17 wherein a regulatory nucleotide sequence is located upstream (5') of the nucleic acid encoding NTR, wherein the regulatory nucleotide sequence has a role in regulating transcription of said nucleic acid encoding NTR.

19. (currently amended) The An herpes simplex virus according to claim 17 or 18 wherein the cassette disrupts a protein coding sequence resulting in inactivation of the respective gene product.

20. (currently amended) The An herpes simplex virus as claimed in any one of claims claim 17 to 19 wherein a transcription product of the cassette is a bi- or poly- cistronic transcript comprising a first cistron encoding the NTR and a second cistron encoding the marker wherein the ribosome binding site is located between said first and second cistrons.

21. (currently amended) The An herpes simplex virus as claimed in any one of claims claim 17 to 20 wherein the ribosome binding site comprises an internal ribosome entry site (IRES).

22. (currently amended) The An herpes simplex virus as claimed in any one of claims claim 17 to 21 wherein the marker is a defined nucleotide sequence encoding a polypeptide.

23. (currently amended) The An herpes simplex virus as claimed in claim 22 wherein the marker comprises the Green Fluorescent Protein (GFP) protein coding sequence or the enhanced Green Fluorescent Protein (EGFP) protein coding sequence.

24. (currently amended) The An herpes simplex virus according to any one of claims claim 17 to 21 wherein the marker comprises a defined nucleotide sequence detectable by hybridisation under high stringency conditions with a corresponding labelled nucleic acid probe.

25. (currently amended) The An herpes simplex virus as claimed in any one of claims claim 17 to 24 wherein the cassette further comprises nucleic acid encoding a polyadenylation sequence located downstream (3') of the nucleic acid encoding the marker.

26. (currently amended) The An herpes simplex virus as claimed in claim 25 wherein the polyadenylation sequence comprises the Simian Virus 40 (SV40) polyadenylation sequence.

27. – 30. (cancelled)

31. (currently amended) A method of lysing or killing tumour cells *in vitro* or *in vivo* comprising the step of administering to a patient in need of treatment an the herpes simplex virus as claimed in any one of claims claim 1 to 26.

32. (currently amended) A medicament, pharmaceutical composition or vaccine comprising an the herpes simplex virus as claimed in any one of claims claim 1 to 26.

33. (currently amended) The A medicament, pharmaceutical composition or vaccine as claimed in claim 32 further comprising a pharmaceutically acceptable carrier, adjuvant or diluent.

34. (currently amended) An herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase (NTR) and wherein said nucleic acid sequence is in at least one of the long repeat regions (R_L) or wherein said herpes simplex virus is non-neurovirulent.

35. (cancelled)

36. (currently amended) A composition comprising ~~a~~the herpes simplex virus ~~according to~~
~~of claim 34 or claim 35~~ and an NTR prodrug.

37. (currently amended) ~~A~~The composition as claimed in claim 36 wherein said NTR
prodrug is CB1954.

38. – 41. (cancelled)

42. (currently amended) A kit of parts comprising a first container having a quantity of
herpes simplex virus ~~according to any one of claims~~claim 1 to 26, 34 or 35 and a second
container having a quantity of an NTR prodrug.

43. – 50. (cancelled)

51. (currently amended) A method for the treatment of a tumour comprising the steps of:

- (i) administering to a patient in need of treatment a therapeutically effective amount
of a herpes simplex virus, wherein the genome of said virus comprises (a) a
nucleic acid sequence encoding a nitroreductase in at least one of the long repeat
regions (R_L), or (b) a nucleic acid sequence encoding a nitroreductase and
wherein the herpes simplex virus is non-neurovirulent; and
- (ii) administering to said patient a therapeutically effective amount of an NTR
prodrug.

52. (cancelled)

53. (currently amended) The method of claim 51 ~~or 52~~ wherein said herpes simplex virus is
capable of killing tumour cells.

54. (currently amended) The ~~virus, kit, use or~~ method as claimed in ~~any one of claims 38 to~~
~~53~~claim 51 wherein said NTR prodrug is CB1954.

55. (original) A method of expressing in vitro or in vivo a nitroreductase, said method comprising the step of infecting at least one cell or tissue of interest with a herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase in at least one of the long repeat regions (R_L), said nitroreductase operably linked to a transcription regulatory sequence.

56. (original) A method of expressing in vitro or in vivo a nitroreductase, said method comprising the step of infecting at least one cell or tissue of interest with a non-neurovirulent herpes simplex virus, wherein the genome of said virus comprises a nucleic acid sequence encoding an heterologous nitroreductase, said nitroreductase operably linked to a transcription regulatory sequence.

57. (original) HSV1716/CMV-NTR/GFP (ECACC accession number 03110501).

58. (new) A method for the treatment of a tumour comprising administering to a patient in need of treatment a therapeutically effective amount of the herpes simplex virus of claim 1.

59. (new) A method for the treatment of a tumour comprising administering to a patient in need of treatment a therapeutically effective amount of the herpes simplex virus of claim 34.

60. (new) A medicament, pharmaceutical composition or vaccine comprising the herpes simplex virus of claim 34.

61. (new) The medicament, pharmaceutical composition or vaccine as claimed in claim 60 further comprising a pharmaceutically acceptable carrier, adjuvant or diluent.

62. (new) A kit of parts comprising a first container having a quantity of herpes simplex virus of claim 34 and a second container having a quantity of an NTR prodrug.

63. (new) The kit as claimed in claim 42 wherein said NTR prodrug is CB1954.

64. (new) The kit as claimed in claim 62 wherein said NTR prodrug is CB1954.